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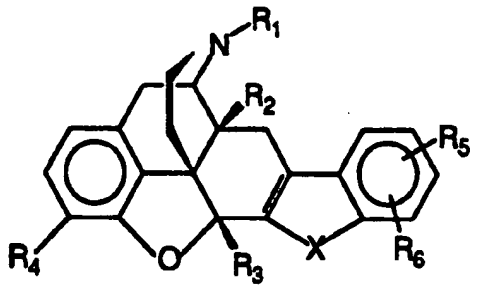
(54) Title: NEW AGONIST COMPOUNDS

(57) Abstract

New morphinane derivatives of formula (I), their pharmaceutically acceptable salts, a process for their preparation and their use in therapy.



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NEW AGONIST COMPOUNDS

Field of the invention

The present invention is related to novel δ opioid receptor agonists as well as to their pharmaceutically acceptable salts, a process for their preparation and their use in the manufacture of pharmaceutical preparations.

Background of the invention

Three major types of opioid receptors, μ, κ and δ, are known and characterized. The identification of different opioid receptors has lead to efforts to develop specific ligands for these receptors. These ligands are known to be useful for at least two purposes:

a) to enable the more complete characterization of these different receptors, and

b) to facilitate the identification of new analgesic drugs.

Analgesic drugs having specificity for an individual opioid receptor type have been demonstrated to have fewer side effects (e.g. respiratory depression, constipation, dependence), and in cases in which tolerance to one drug has developed, a second drug with different opioid receptor specificity may be effective. For example the successfull substitution of DADLE (intrathecal application), a partially δ-selective analgesic peptide, for morphine in a human cancer patient with morphine tolerance has been demonstrated (E.S. Krames et al., Pain, Vol. 24:205-209,1986). Evidence that a δ-selective agonist could be a potent analgesic with less tolerance and dependence liability was presented by Frederickson et al. (Science, Vol. 211:603-605,1981). The peptide, [D-Ala^2,N-MeMet^5]enkephalin amide or "metkephamid", was hundred fold more potent than

morphine in the hot-plate test for analgesia after i. c. v. (intracerebral ventricular) administration. Naloxone precipitation of withdrawal after chronic administration of metkephamid and morphine in rats showed that metkephamid-treated animals exhibited fewer withdrawal symptoms than those given morphine, scoring only a little above the saline control group. Metkephamid produced substantially less respiratory depression than morphine.

Another δ-selective peptide, [D-Pen^2, D-Pen^5]enkephalin (DPDPE) produces potent analgesic effects while showing little if any respiratory depression (C.N. May, Br.J. Pharmacol., Vol.98:903-913,1989). DPDPE was found not to produce gastrointestinal side effects (e.g. constipation) (T.F.Burks, Life Sci., Vol.43:2177-2181,1988). Since it is desireable that analgesics are stable against peptidases and are capable of entering the CNS easily, non-peptide analgesics are much more valuable.

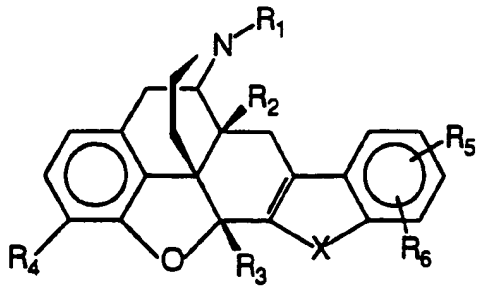
Prior art

Recently a non-peptide, δ-selective opioid agonist, BW373U86 - a piperazine derivative, has been disclosed. BW 373U86 is reported to be a potent analgesic which does not produce physical dependence (P.H.K. Lee et al., J.Pharmacol.Exp.Ther., Vol. 267:983-987,1993).

An undesired side effect of this compound is that it produces convulsions in animals. The convulsions were antagonized by the δ-selective opioid antagonist naltrindole.

Outline of the invention

The present invention provides novel analgesic compounds of the formula I



(I)

wherein

R_1 represents C_1-C_6 alkyl or hydrogen;

R_2 represents hydrogen, hydroxy, C_1-C_6 alkoxy; C_1-C_6 alkenyloxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_7-C_{16} arylalkenyloxy wherein the aryl is C_6-C_{10} aryl and the alkenyloxy is C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy, C_1-C_6 alkenoyloxy, C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl, and the alkanoyloxy is C_1-C_6 alkanoyloxy;

R_3 represents hydrogen, C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; hydroxy(C_1-C_6)alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2H; CO_2(C_1-C_6 alkyl);

R_4 is hydrogen, hydroxy; C_1-C_6 alkoxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 akyloxy; C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy;

C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy; alkyloxyalkoxy wherein alkyloxy is C_1-C_4 alkyloxy and alkoxy is C_1-C_6 alkoxy;

R_5 and R_6 each independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C_1-C_6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; $CO_2(C_1$-C_6 alkyl); $CONH_2$; $CONH(C_1$-C_6 alkyl); $CON(C_1$-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino; C_5-C_6 cycloalkylamino; SH; SO_3H; $SO_3(C_1$-C_6 alkyl); $SO_2(C_1$-C_6 alkyl); SO_2NH_2; $SO_2NH(C_1$-C_6 alkyl); $SO_2NH(C_7$-C_{16} arylalkyl); $SO(C_1$-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, $CO(C_1$-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H; $SO_3(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), $SO(C_1$-C_6 alkyl), and

X represents oxygen; sulfur; CH=CH; or NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl, and

wherein aryl is unsubstituted or mono-, di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, $CONH_2$ $CO_2(C_1$-C_3 alkyl), $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl)$_2$ $CO(C_1$-C_3 alkyl); amino; (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6

cycloalkylamino, (C_1-C_3 alkanoyl)amido, SH, SO_3H, SO_3(C_1-C_3 alkyl), SO_2(C_1-C_3 alkyl), SO(C_1-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio;

with the proviso that when R_2 is hydroxy, R_3 cannot be hydrogen;

the compounds 6,7-Dehydro-4,5α-epoxy-3,14-dimethoxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-7'-bromo-6,7-2',3'-indolomorphinan;

3,14-Diacetocy-6,7-dehydro-4,5α-epoxy-17-methyl-6,7-2',3'-indolomorphinan;

14-Acetoxy-6,7-dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;

14-Benzyloxy-6,7-dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;
being excluded,

and the pharmacologically acceptable salts of the compounds of the formula (I).

Aryl may be unsubstituted or mono-, di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, $CONH_2$, $CO_2(C_1$-C_3 alkyl), $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl)$_2$, $CO(C_1$-C_3 alkyl); amino; (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6 cycloalkylamino; (C_1-C_3 alkanoyl)amido, SH, SO_3H, $SO_3(C_1$-C_3 alkyl), $SO_2(C_1$-C_3 alkyl), $SO(C_1$-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio.

The above given definition for aryl is valid for all substituents in the present application where aryl is present.

Pharmaceutically and pharmacologically acceptable salts of the compounds of formula I include suitable inorganic salts and organic salts which can be used according to the invention. Examples of inorganic salts which can be used are HCl salt, HBr salt, sulfuric acid salt and phosphoric acid salt. Examples of organic salts which can be used according to the invention are methanesulfonic acid salt, salicylic acid salt, fumaric acid salt, maleic acid salt, succinic acid salt, aspartic acid salt, citric acid salt, oxalic acid salt and orotic acid salt. These examples are however not in any way limiting the salts which could be used according to the invention.

The novel δ-selective morphinane derivatives of the formula I are useful as analgesics without having dependence liability. They may be administered parenterally or non-parenterally. Specific routes of administration include oral, rectal, topical, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, intrathecal, transdermal, intraartherial, bronchial, lymphatic and intrauterine administration. Formulations suitable for parenteral and oral administration are preferred.

In a preferred embodiment

R_1 is selected from hydrogen, methyl, ethyl, n-propyl or isopropyl;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO_2, CN, CF_3, CH_3, OCH_3, allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R_3 is selected from hydrogen, methyl, ethyl, benzyl or allyl;

R_4 is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R_5 and R_6 are each and independently selected from hydrogen, nitro, cyano, chloro, fluoro, bromo, trifluoromethyl, CO_2H, CO_2CH_3, $CONH_2$, $CONH\,CH_3$, SH, SO_2NH_2, $N(CH_3)_2$, $SO_2\,CH_3$ and

X is selected from O, NH, NCH_3, N-benzyl, N-allyl.

In an especially preferred embodiment

R_1 is CH_3;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy or benzyloxy substituted in the aromatic ring with chlorine

R_3 is selected from hydrogen or CH_3;

R_4 is hydroxy;

R_5 and R_6 are each and independently selected from hydrogen, CO_2H, $CONH_2$, SO_2NH_2, or SO_2CH_3; and

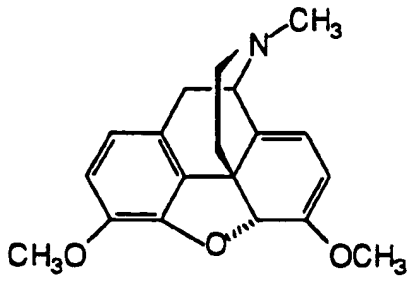
X is selected from O or NH.

The best mode known at present is to use the compound according to Example 1.

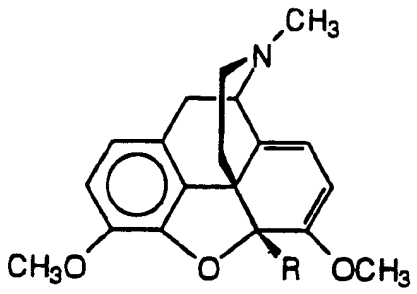
Preparation of the compounds

The compounds represented by formula (I) wherein R_3 is C_1-C_6 alkyl, C_7-C_{16} aralkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl); C_1-C_6 alkanoyl; may be obtained by the following methods:

Thebaine of the formula



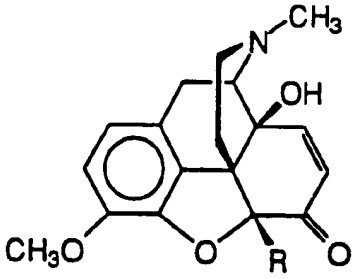
is being treated with dialkylsulfates, fluorosulfonic acid alkyl esters, alkylsulfonic acid alkyl esters, arylsulfonic acid alkylesters, alkyl halides, alkenyl halides, aralkyl halides, alkylsulfonic acid aralkyl esters, arylsulfonic acid aralkyl esters, arylalkenyl halides or chloroformates, in solvents such as tetrahydrofurane or diethyl ether using a strong base such as n-butyl lithium, lithium diethyl amide or lithium diisopropyl amide at low temperatures (-20 to -80 °C) (s. Boden et al., J.Org.Chem., Vol.47:1347-1349, 1982, Schmidhammer et al., Helv.Chim. Acta. Vol.71:642-647,1988, Gates et al., J.Org. Chem. Vol. 54; 972-974, 1984), giving compounds of formula (II),



(II)

wherein R is C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl, wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

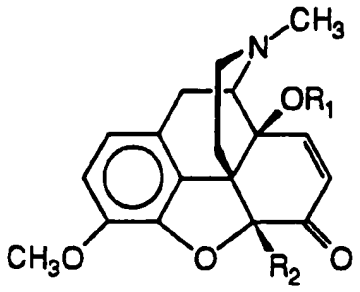
The 5-substituted thebaine derivatives (formula II) or thebaine are converted into the corresponding 14-hydroxycodeinones (compounds of formula III)



(III)

wherein R is as defined above or being hydrogen, by reaction with performic acid (H. Schmidhammer et al., Helv.Chim.Acta, Vol. 71:1801-1804, 1988) or m-chloroperbenzoic acid, at a temperature between 0 and 60 ° C. The preferred procedure is the reaction with performic acid at 0-10°C (H.Schmidhammer et.al., Helv. Chim. Acta. Vol. 71:1801-1804, 1988). These 14-hydroxycodeinones are being treated with dialkyl sulfates, alkyl halides, alkenyl halides, arylalkyl halides, arylalkenyl halides or chloroformates, in solvents such as N,N-dimethyl

formamide or tetrahydrofurane using a strong base such as sodium hydride, potassium hydride or sodium amide giving compounds of formula (IV)



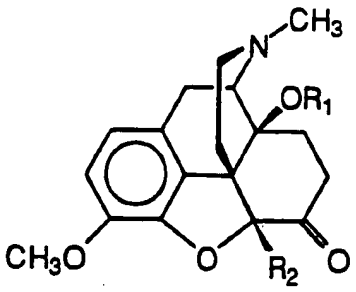
(IV)

wherein

R_1 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl, C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl, C_7-C_{16} arylalkenoyl wherein the aryl is C_6-C_{10} aryl and the alkenoyl is C_1-C_6 alkenoyl;

R_2 is hydrogen; C_1-C_6 alkyl; C_1-C_6 alkenyl C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

which compounds in turn are reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal and solvents such as methanol, ethanol, or glacial acetic acid to give compounds of formula (V)



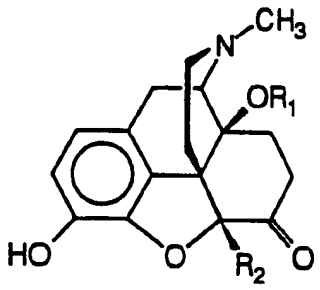
(V)

wherein

R_1 is C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl;

R_2 is hydrogen; C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; $CO_2(C_1$-C_6 alkyl);

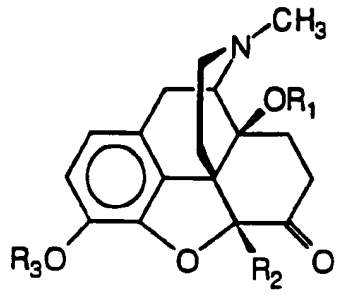
Ether cleavage of these compounds using boron tribromide (in a solvent such as dichloro methane or chloroform) at about 0°C, 48 % hydrobromic acid (reflux), or other well known reagents gives phenolic compounds of formula (VI),



(VI)

wherein R_1 and R_2 are as defined above in formula (V).

Alkylation using alkyl halides, alkyl sulfates, sulfonic acid esters, aralkyl halides, arylalkenyl halides, or acylation using carbonic acid chlorides, carbonic acid anhydrides, or carbonic acid esters affords compounds of formula (VII)

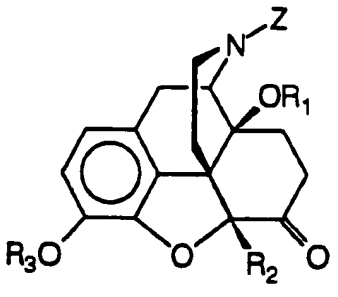


(VII)

wherein R_1 and R_2 are as definded above in formula (V), and

R_3 is C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl, alkyloxyalkyl wherein alkyloxy is C_1-C_4 alkyloxy and alkyl is C_1-C_6 alkyl,

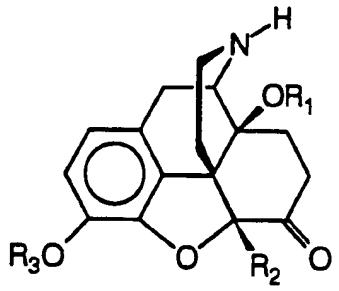
which after N-demethylation using for instance chloroformates or cyanogen bromide followed by cleavage of the corresponding carbamates or N-cyano compounds (compounds of formula VIII)



(VIII)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII),

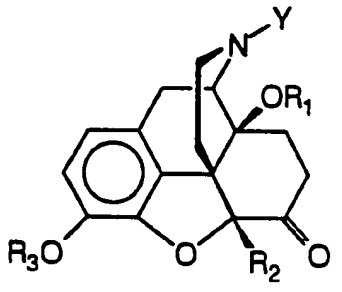
and Z is for instance $CO_2CH=CH_2$, $CO_2CHClCH_3$, $CO_2CH_2CH_3$, CO_2Ph, $CO_2CH_2CCl_3$ or CN by treatment with the adequate reagent such as aqueous acid, alkali, hydrazine, zinc, alcohol or the like N-nor derivatives of formula (IX)



(IX)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII).

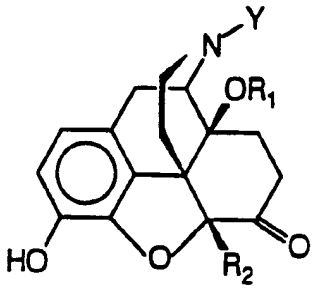
N-alkylation can be accomplished with alkyl halide or dialkyl sulfate in solvents such as dichloro methane, chloroform or N,N-dimethyl formamide in the presence of a base such as sodium hydrogen carbonate or potassium carbonate to yield derivatives of formula (X)



(X)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII), and Y is methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, tert-butyl, 2-pentyl, 3-pentyl, 2-hexyl or 3-hexyl.

Ether cleavage can be carried out as described for compounds of formula (V) giving derivatives of formula (XI)



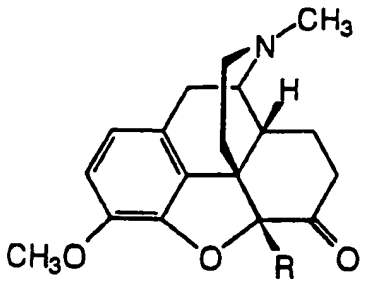
(XI)

wherein R_1 and R_2 are as defined above in formula (V), and Y is as defined above in formula (X).

Compounds according to formula (I) wherein R_2 is hydroxy may be obtained from compounds of the formula (III) wherein R is defined as above. These compounds can be reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal and solvents such as methanol, ethanol, or glacial acetic acid to give compounds of formula (V) wherein R_1 is hydrogen and R_2 is as defined above.

The following reaction sequence and procedures leading to compounds of formula (VI),(VII),(VIII),(IX),(X), and (XI) wherein R_1 is hydrogen and wherein R_2 and R_3 are as defined above in formula (V) and (VII), is analogous to the reaction sequence and procedures described above. Further conversion into compounds of the formula (I) wherein R_2 is hydroxy is described below.

Compounds of the formula (I) wherein R_2 is hydrogen may be obtained from compounds of the formula (II) wherein R is as defined above. Catalytic hydrogenation followed by acid hydrolysis (s. Boden et al., J. Org. Chem. Vol. 47: 1347-1349, 1982) gives compounds of the formula (XII)



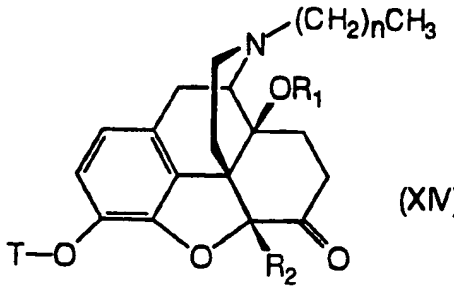
(XII)

(XII a): R= H (dihydrocodeinone)

wherein R is as defined above in formula (II).

Compounds of the formula (XII) and (XII a) (Mannich and Löwenheim, Arch. Pharm., Vol. 258:295, 1920) can be converted into compounds of the formula (V), (VI), (VII), (VIII), (IX), (X) and (XI) wherein the substitutent in position 14 is hydrogen and R_2 and R_3 are as defined above in formula (V) and (VII), similary as described above. Further conversion into compounds of the formula (I) wherein R_2 is hydrogen is described below.

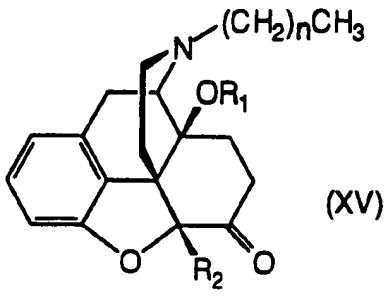
Compounds of the formula (I) wherein R_4 is hydrogen may be prepared from compounds of the formulas (VI) or (XI) by alkylation with 5-chloro-1-phenyl-1H-tetrazole to give the corresponding phenyltetrazolyl ethers of the formula (XIV)



(XIV)

wherein R_1 and R_2 are defined as above, n is 0-5 and T is phenyltetrazolyl.

Catalytic hydrogenation may afford (H. Schmidhammer et al., J. Med. Chem. Vol. 27: 1575-1579, 1984), compounds of the formula (XV)



(XV)

wherein R_1 and R_2 are as defined above and n is 0-5.

Compounds according to the formula (I) wherein R_2 is as defined above and X represents NH are obtained by reaction of compounds of formula (VI), (VII), (IX), (X), (XI) or (XV) with phenylhydrazine or substituted phenylhydrazine in solvents such as methanol, ethanol or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr. Phenylhydrazine substituted at the aromatic ring with halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, nitro, cyano, thiocyanato, trifluoromethyl, CO_2H, $CO_2(C_1$-C_6 alkyl), $CONH_2$, $CONH(C_1$-C_6 alkyl), $CON(C_1$-C_6 alkyl)$_2$,SO_2NH_2,$SO_2(C_1$-C_6 alkyl) or the like may be employed. The reaction may be carried out at a temperature between 20 and 160 °C, preferably between 20 and 80 °C.

Compounds of formula (I) wherein R_3 is as defined above and X represents oxygen are obtained by reaction of compounds of formula (VI), (VII), (IX), (X), (XI) or (XV) with O-phenylhydroxylamine or substituted (at the aromatic ring) O-phenylhydroxylamine in solvents such as methanol, ethanol, or glacial acetic acid in the presence of methanesulfonic acid, HCl or HBr. O-Phenylhydroxylamine substituted at the aromatic ring with halogen, C_1-C_6 alkyl, amino, nitro, cyano,

thiocyanato, trifluoromethyl, CO_2H, $CO_2(C_1\text{-}C_6$ alkyl), $CONH_2$, $CONH(C_1\text{-}C_6$ alkyl), $CON(C_1\text{-}C_6$ alkyl)$_2$,SO_2NH_2,$SO_2(C_1\text{-}C_6$ alkyl) or the like may be employed.

The following examples describe in detail the preparation of the compounds according to the invention.

Example 1

Synthesis of 6,7-Dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5,17-dimethyl-6,7-2',3'-indolomorphinan (compound 1).

A mixture of 14-ethoxymetopon (H. Schmidhammer et al. Helv. Chim Acta. Vol. 73: 1784-1787, 1990) (500 mg, 1.45 mmol), phenylhydrazaine hydrochloride (340 mg, 2.35 mmol) and 10 ml of glacial acetic acid was refluxed for 48 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with H_2O (3x15 ml), dried over Na_2SO_4 and evaporated. The resulting residue (546 mg orange-brown foam) was crystallized with MeOH to yield 322 mg of the title compound which was further purified by column chromatography (alumina basic grade IV, elution with a) CH_2Cl_2, b) CH_2Cl_2/MeOH 99:1). After evaporation of the corresponding fractions, 237 mg of slightly yellow crystals were obtained. Recrystallization from MeOH yielded 116 mg (24%) of pure title compound 1. M.p. 165-167 °C. IR (KBr): 3285 (NH, OH)cm^{-1}. CI-MS:m/z 417 (M^+ + 1). ^{1}H-NMR($CDCl_3$): δ 8.15 (s, NH, OH), 7.35 (d, J = 8 Hz, 1 arom. H), 7.26 (d, J = 8 Hz, 1 arom. H), 7.13 (t, J = 8 Hz, 1 arom. H), 7.01 (t, J = 8 Hz, 1 arom. H), 6.64 (d, J = 8 Hz, 1 arom. H), 6.55 (d. J = 8 Hz, 1 arom. H), 2.40 (s, CH_3N), 1.94 (s, CH_3-C(5)),

1.02 (t. J = 7 Hz, 3H, CH_3CH_2O). Analysis calculated for $C_{26}H_{28}N_2O_3$. (480.60): 69.98, H 7.55, N 5.83; found: C 70.23, H 7.40, N 5.87.

Example 2

Synthesis of 6,7-Dehydro-4,5α-epoxy-3,14-dimethoxy-5,17-dimethyl-6,7-2',3'-indolomorphinan (compound 2).

A mixture of 5,14-O-dimethyloxycodone (H. Schmidhammer et al., Helv. Chim. Acta Vol. 73: 1784-1787, 1990) (300 mg, 0.87 mmol), phenylhydrazine hydrochloride (189 mg, 1.31 mmol), methanesulfonic acid (84 mg, 0.87 mmol), and 12 ml of glacial acetic acid was refluxed for 17 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with H_2O (3x10 ml), dried over Na_2SO_4 and evaporated. The resulting residue (380 mg yellowish crystals) was recrystallized from MeOH to yield 336 mg (93%) of pure title compound 2 as slightly yellow crystals. M.p. 218-221°C. (KBr): 3800 (NH) cm^{-1}. CI-MS: m/z 417 (M^++1). ^{1}H-NMR ($CDCl_3$): δ 8.30 (s, NH), 7.48 (d, J= 8 Hz, 1 arom. H), 7.39 (d,J=8 Hz, 1 arom. H), 7.12 (t, J=8 Hz, 1 arom. H), 7.03 (t, J=8 Hz, 1 arom, H), 6.58 (s, 2 arom. H), 3.73 (s, OCH_3-C(3)), 3.28 (s, OCH_3-C(14)), 2.45 (s, NCH_3), 1.87 (s, CH_3-C(5)). Analysis calculated for $C_{26}H_{28}N_2O_3$. 2 MeOH (480.60): C 69.98, H 7.55, N5.83; found C 70.19, H 7.41, N 5.95.

Example 3

Synthesis of 6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5,17-dimethyl-6,7-2'3'-indolomorphinan (compound 3).

A mixture of 14-methoxymetopon hydrobromide (H. Schmidhammer et al., Helv. Chim. Acta Vol. 73: 1784-1787, 1900) (500mg, 1.22 mmol) phenylhydrazine hydrochloride (211 mg, 1.46 mmol), and 10 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with H_2O (3 x 15 ml), dried over Na_2SO_4 and evaporated. The resulting residue (455 mg slightly grey foam) was crystallized from MeOH to give 330 mg (67%) of pure title compound 3. M. p. 273-276°C (dec.). IR (KBr): 3300 (NH, OH) cm^{-1}. CI-MS: M/Z 403 (M^++1). ^{1}H-NMR (DMSO-d_6): δ 11.10 and 8.78 (2 s, NH, OH), 7.32 (dxd, J= 8 HZ, 2 arom. H.) 7.07 (t, J=8 HZ, 1 arom. H), 6.91 (t, J=8 HZ, 1 arom. H), 6.44 (s, 2 arom. H), 3.32 (s. OCH_3), 2.33 (s, NCH_3), 1.81 (s, CH_3-C(5)). Analysis calculated for $C_{25}H_{26}N_2O_3$. 2 MeOH (466.56):C 69.50, H 7.35, N 6.01; found: C 69.78, H 7.38, N 6.09.

Example 4

Synthesis of 6,7-Dehydro-4,5α-epoxy-3,14-dihydroxy-5,17-dimethyl-6,7-2'3'-indolomorphinan Hydrobromide (compound 4).

A mixture of 14-hydroxymetopon hydrobromide (H.Schmidhammer et al., Helv. Chim. Acta Vol. 71: 1801-1804, 1988) (450 mg, 0.95 mmol), phenylhydrazine hydrochloride (280 mg, 1.93 mmol), and 15 ml of glacial acetic acid was refluxed for 20 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x60 ml). The combined organic layers were washed with H_2O (3x60 ml) and brine, dried over Na_2SO_4 and evaporated. The resulting residue (392 mg of a brownish foam) was dissolved in glacial acetic acid and treated with 48% HBr. The crystals were collected and recrystallized from glacial acetic acid to yield 132 mg (25%) of the title compound 4 as colorless

crystals. M.p. >250°C (dec.). IR (KBr)3300 (˜NH,OH)cm^{-1}. CI-MS:m/z 389(M˙ +1). ^{1}H-NMR (DMSO-d_6): δ 11.28 (s, NH), 9.19 (s, OH-C(3)), 9.09 (broad s, ˜NH), 7.10 (m, 4 arom. H), 6.56 (s, 2 arom. H)6.12(s, OH-C(14)),2.88 (s, NCH_3), 1.88 (s, CH_3-C(5)). Analysis calculated for $C_{24}H_{24}N_2O_3$ x HBr x 0.1 H_2O (489.20); C 58.93, H 5.60, N 5.73, Br 16.33;
Found: C 59.01, H 5.55, N 5.56, Br 16.17.

Example 5

Synthesis of 7,8-Dehydro-4,5α-epoxy-14-hydroxy-3-methoxy-5,17-dimethyl-6,7-2'3'-indolomorphinan Hydrobromide (compound 5).

A mixture of 5-methyloxycodon (H.Schmidhammer et al., Helv. Chim. Acta, Vol. 71: 1801-1804, 1988) (350 mg, 0.72 mmol), phenylhydrazine hydrochloride (260 mg, 1.79 mmol), and 15 ml of glacial acetic acid was refluxed for 18 h. After cooling, the reaction mixture was poured on ice, alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x50 ml). The combined organic layers were washed with H_2O (3x60 ml) and brine, dried over Na_2SO_4 and evaporated. The resulting residue (365 mg brownish foam) was dissolved in glacial acetic acid and treated with 48% HBr. The crystals were collected and recrystallized from glacial acetic acid to give 130 mg (25%) of pure title compound 5. HBr. M.p. >260°C (dec.). IR (KBr): 3406, 3396, 3242 (NH, ˜NH, OH)cm^{-1}. CI-MS: m/z 403(M˙ +1) ^{1}H-NMR (DMSO-d_6): δ 11.34 (s, NH), 9.20 (broad s ˜NH), 7.05 (m, 4 arom. H), 6.76 (d, J=8,3 Hz, 1 arom. H). 6.69 (d, J=8.3 HZ, 1 arom. H), 6.17 (s,OH-C(14)), 3.65 (s,OCH_3), 2.90(s, NCH_3)1.89 (s,CH_3-C(5)). Analysis calculated for $C_{25}H_{26}N_2O_3$ x HBr x 0.9H_2O (499.63): C 60.10, H 5.81, N 5.61, Br 15.99;
Found: C 60.11, H 5.97, N 5.55, Br 16.02.

Example 6

Synthesis of 6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan (compound 7).

A solution of 4,5α-epoxy-3,14-dimethoxy-5-methylmorphinan-6-one hydrochloride (H. Schmidhammer et al., Helv. Chim. Acta Vol. 77: 1585-1589,1994) (1.0 g, 2.73 mmol) in 3.5 ml of 48% HBr was refluxed for 15 min. After cooling, the now brown solution was evaporated, the residue treated with MeOH and again evaporated (this operation was repeated once). The oily residue was crystallized from MeOH to yield 713 mg (66%) of colorless 4,5a-epoxy-3-hydroxy-14-methoxy-5-methylmorphinan-6-one hydrobromide (compound 6). M.p.>230°C (dec.). IR (KBr): 3545 and 3495 ($^{\cdot}$NH, OH), 1720 (CO)cm^{-1}. CI-MS:m/z 316($M^{\cdot}$+1). ^{1}H-NMR(DMSO-d_6):δ 9.37 (s,OH), 8.65 (broad s, $^{\cdot}NH_2$), 6.64 (dd, J=8.2, 8.2 Hz, 2 arom. H), 3.36 (s, OCH_3-C(14)), 1.48 (s,CH_3-C(5)). Analysis calculated for $C_{18}H_{21}NO_4$. HBr. MeOH(428.33):C 53.28, H 6.12, N 3.27; found: C 53.12, H 5.97, N 3.32.

A mixture of 4,5α-epoxy-3-hydroxy-14-methoxy-5-methylmorphinan-6-one hydrobromide (compound 6, 1.2 g, 3.03 mmol), phenylhydrazine hydrochloride (548 mg, 3.79 mmol), and 15 ml of glacial acetic acid was refluxed for 4 h. After cooling, the reaction mixture was evaporated to give a brownish solid (2.14 g) which was refluxed in 10 ml of MeOH for 5 min and the refrigerated. The solid was isolated (the mother liquor of this isolation was further processed, see below), dissolved in H_2O and alkalized with conc. NH_4OH. The precipitation was isolated to yield 569 mg (70%) of pure title compound 7. M.p.>270°C (dec.). IR (KBr): 3395 and 3380 (NH, OH)cm^{-1}. EI-MS: m/z 388 ($M^{\cdot}$). Analysis calculated for $C_{24}H_{24}N_2O_3$ x 0.3 H_2O (393.87): C 73.19, H 6.30, N 7.11; found: C 73.08, H 6.03, N 7.07.

Above mother liquor was evaporated and the resulting residue (566 mg) treated with 2 ml of hot MeOH to afford (after refrigeration) 201 mg (14%) of the title compound 7.HBr. M.p.>230° (dec.). ^{1}H-NMR of 7.HBr (DMSO-d_6):δ 11.30 (s, NH), 9.13 and 8.50 (2 s, NH, OH), 7.33 (dd, J=7.4, 7.4 Hz, 2 arom. H), 7.08 (t, J=7.4 Hz, 1 arom. H) 6.93(t, J=7.4 Hz, 1 arom.H), 6.57 (s, 2 arom. H), 3.32 (s, CH_3O-C(14)), 1.84 (s, CH_3-C(5)).

Example 7

Synthesis of 6,7-Dehydro-4,5α-epoxy-3-hydroxy-5,17-dimethyl-14-n-propyloxy-6,7-2',3'-indolomorphinan methane sulfonate (compound 11).

A solution of 14-hydroxy-5-methylcodeinone (H. Schmidhammer et al., Helv. Chim. Acta Vol. 71: 1801-1804, 1988) (5.0 g, 15.27 mmol) in 50 ml of anhydrous N,N-dimethyl formamide was cooled to 0-5°C. Sodium hydride (1.47 g, 15.27 mmol; obtained from 2,7 g of 60% sodium hydride dispersion in oil by washings with petroleum ether) was added under nitrogen atmosphere, and the resulting mixture stirred for 20 min. Then allyl bromide (2.64 ml, 30.54 mmol) was added in one portion, and stirring was continued at 0-5°C for 30 min. Excess sodium hydride was desroyed carefully with small pieces of ice, then the mixture was poured on 150 ml ice/H_2O. After extractions with CH_2Cl_2 (3x50 ml), the combined organic layers were washed with H_2O (3x100 ml) and brine, dried over Na_2SO_4 and evaporated to yield 6.43 g of a slightly yellow crystalline residue. Treatment with boiling ethanol (6 ml) gave (after refrigeration) 3.01 g (54%) of 14-allyloxy-5-methylcodeinone (compound 8). M.p. 136-137°C. IR(KBr): 1664 (CO)cm^{-1}. CI-MS:m/z 368(M^++1). ^{1}H-NMR (DMSO-d_6): δ 6.78 (d, J=10.2 Hz, 1 olef.H.), 6.62 (d, J=8.2 Hz, 1arom.H), 6.54 (d, J=8.2 Hz, 1 arom. H), 6.09 (d, J=10.2 Hz, 1 olef.H), 5.87 (m, 1 olef. H), 5.15 (m, 2 olef.H), 3.79 (s, CH_3O), 2.44 (s, CH_3N), 1.71 (s, CH_3-

C(5)). Analysis calculated for $C_{22}H_{25}NO_4$(367.45): C 71.91, H 6.86, N 3.81; found: C 71.69, H 7.03, N 3.75.

A mixture of 14-allyloxy-5-methylcodeinone (compound 8;3,2 g, 10.64 mmol), 196 mg of 10% Pd/C catalyst, and 100 ml of ethanol was hydrogenated at 30 psi and room temperature for 3 h. The catalyst was filtered off and the filtrate evaporated. The residue (3.79 g colorless oil) was crystallized from ethanol to yield 2.93 g (74%) of 7,8-dihydro-5-methyl-14-n-propyloxycodeinone (compound 9). M.p. 102-104°C IR (KBr): 1718 (CO) cm^{-1}. CI-MS:m/z 372 (M^++1). ^{1}H-NMR (DMSO-d_6): δ 6.50 (dd, J=8,8 Hz, 2 arom. H), 4.76 (s, CH_3O), 2.35 (s, CH_3N), 1.61 (s, CH_3.C(5)), 1.00 (t, J=7 Hz, CH_3). Analysis calculated for $C_{22}H_{29}NO_4$. 0.2 EtOH (380.69): C 70.67, H 8.00, N 3.68; found: C 70.64, H 7.72, N 3.69.

A 1 M solution of boron tribomide in CH_2Cl_2 (54 ml) was added at once to an ice-cooled solution of 7,8-dihydro-5-methyl-14-n-propyloxycodeinone (compound 9; 2.7 g, 7.27 mmol) in 370 ml of CH_2Cl_2. After 2 h stirring at 0-5°C, a mixture of 90 g of ice and 20 ml of conc. NH_4OH was added. The resulting mixture was stirred at room temperature for 30 min and then extracted with CH_2Cl_2 (3x200 ml). The combined organic layers were washed with brine (300 ml), dried over Na_2SO_4 and evaporated. The residue (2.4 g slightly brown foam) was crystallized from MeOH to give 1.48 g (57%) of 4,5α-epoxy-3-hydroxy-5,17-dimethyl-14-n-propyloxymorphinan-6-one (compound 10) as slightly brown crystals. An analytical sample was obtained by recrystallization of a small amount from MeOH. M.p. 193-195°C. IR (KBr): 3376 (OH), 1726 (CO) cm^{-1}. EI-MS: m/z 357 (M^+). ^{1}H-NMR ($CDCl_3$): δ 6.67 (d,J = 8.1 Hz, 1 arom. H), 6.52 (d,J = 8.1 Hz, 1 arom. H), 1.57 (s, CH_3-C(5)), 0.96 (t,J = 7.2 Hz, CH_3). Analysis calculated for $C_{21}H_{27}NO_4$ (357.43): C 70.56, H 7.61, N 3.92; found: C 70.50, H 7.88, N 3.92.

A mixture of 4,5α-epoxy-3-hydroxy-5,17-dimethyl-14-n-propyloxymorphinan-6-one (compound 10; 350 mg, 0.97 mmol), phenylhydrazine hydrochloride 212 mg, 1.47 mmol), and 20 ml of glacial acetic acid was refluxed for 24 h. After cooling, the reaction mixture was poured on ice and alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3x40 ml). The combined organic layers were washed with H_2O (3x50 ml) and brine, dried over Na_2SO_4 and evaporated. The resulting residue (276 mg brown foam) was dissolved in MeOH and treated with methanesulfonic acid to give 180 mg of the title compound. Recrystallization from MeOH yielded 44 mg (9%) of pure compound 11. M. p. > 270°C. IR (KBr): 3203 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ 11.29 (s, NH), 9.13 (s, OH), 8.47 (broad s, NH), 7.15 (m, 4 arom. H), 6.58 (s, 2 arom. H), 2.97 (s. NCH_3), 1.86 (s, CH_3-C(5)), 0.57 (t,J = 7.3 Hz, CH_3). Analysis calculated for $C_{27}H_{30}N_2O_3$. CH_3SO_3H. 0,7 H_2O (539.27): C 62.36, H 6.62, N 5.19, S 5.95; found: C 62.36, H 6.50, N 5.20, S 6.02.

Example 8

Synthesis of 6,7-Dehydro-4,5α-epoxy-14-ethoxy-3-methoxy-17-methyl-6,7-2',3'-indolomorphinan. (Compound 12).

A mixture of 14-O-ethyloxycydone hydrochloride (R.J. Kobylecki et al, J. Med. Chem. Vol. 25: 116-120, 1982) (580 mg, 1.53 mmol), phenylhydrazine hydrochloride (265 mg, 1.83 mmol), and 8 ml of glacial acetic acid was stirred for five days at room temperature. The mixture was poured on ice, alkalized with conc. NH_4OH and extractred with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with H_2O (3x15 ml), dried over Na_2SO_4 and evaporated. The resulting residue (590 mg slightly orange foam) was crystallized from MeOH to yield 360 mg (56%) of compound 12. M.p. 143-145°C (dec.) IR (Kbr): 3260 (NH)cm^{-1}. Cl-MS:m/z 417 (M^+ + 1). ^{1}H-NMR($CDCl_3$): δ 8.22 (s, NH, OH), 7.39 (d, J = 8 Hz, 1

arom. H), 7.30 (d, J = 8 Hz, 1 arom. H), 7.15 (t, J = 8 Hz, 1 arom. H), 1 arom. H), 7.02 (t, J = 8 Hz, 1 arom. H), 6.58 (s, 2 arom. H), 5.66 (s, H-C(5)), 3.74 (s, CH_3O), 2.39 (s, CH_3N), 1.01 (t, J = 7 Hz, 3H, CH_3CH_2O). Analysis calculated for $C_{26}H_{28}N_2O_3$. 1.0 MeOH (448.56): C 72.30, H 7.19, N 6.25; found: C 72.50, H 6.93, N 6.58.

Example 9

Synthesis of 6,7-Dehydro-4,5α-epoxy-14-ethoxy-17-isopropyl-3-methoxy-5-methyl-6,7-2',3'-benzo[b]furanomorphinan (compound 14).

A mixture of 14-ethoxy-7,8-dihydronorcodeinone hydrochloride (R.J. Kobylecki et al., J. Med. Chem., Vol. 25: 116, 1982) (1.5g, 4.1 mmol), potassium carbonate (3.2 g, 22.52 mmol), isopropyl bromide (1.2 ml, 13.31 mmol), and anhydrous N,N-dimethylformamide (15 ml) was stirred at 50°C (bath temperature) for 7 days. The inorganic solid was filtered off, the filtrate evaporated, dissolved in 40 ml of CH_2Cl_2 and washed with H_2O (3x30 ml). The organic phase was dried over Na_2SO_4 and evaporated to give 1.79 colorless crystals. Recrystallization from 1.7 ml of MeOH afforded 1.15 g (76%) of compound 13 (=14-ethoxy-17-isopropyl-7,8-dihydronorcodeinone). M.p. 188-190°C. IR (Kbr): 1718 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.65 (d, J = 8.3 Hz, 1 arom. H), 6.56 (d, J = 8.3 Hz, 1 arom H), 4.62 (s, H-C(5)), 3.87 (s, CH_3O), 1.23 (t, J = 6.8 Hz, 3 H, CH_3CH_2O). Cl-MS (m7z 372 (M^++1). Analysis calculated for $C_{22}H_{29}NO_4$ x 0.2 MeOH (377.89): C 70.56, H 7.95, N 3.71; found: C 70.43, H 7.64, N 3.70.

A mixture of compound 13 (250 mg, 0.67 mmol), O-phenylhydroxylamine hydrochloride (196 mg, 1.34 mmol), methanesulfonic acid (0.1 ml) and anhydrous methanol (6 ml) was refluxed for 6 days. After cooling, the solution was alkalized

with conc. NH_4OH and extracted with CH_2Cl_2 (3x 50 ml). The combined organic layers were washed with H_2O (3x50 ml) and brine (30 ml) and evaporated to give 217 mg of a brown foam which was crystallized from methanol to afford 102 mg of brownish crystal which were recrystallized from methanol to yield 33 mg (11%) of pure compound 14. M.p. 199-201°C. ^1H NMR ($CDCl_3$): δ 7.10-6.42 (m, 6 arom. H), 4.90 (s, H-C(5)), 3.98 (s, 3 H, CH_3O), 1.29 (t, J = 6.7 Hz, 3 H, CH_3CH_2O), 1.08 (dd, J = 6.1 Hz, 2 CH_3). CI-MS: m/z 446 (M^++1). Analysis calculated for $C_{28}H_{31}NO_4 \times 1.8\ H_2O$ (477.99): C 70.63, H 7.30, N 2.93; C 70.33, H 7.00, N 2.84.

Pharmaceutical preparations

For the preparation of a pharmaceutical formulation, the active ingredient may be formulated to an injection, capsule, tablet, suppository, solution or the like. Oral formulation and injection are preferably employed. The pharmaceutical formulation may comprise the δ-selective agonist alone or may also comprise expedients such as stabilizers, buffering agents, diluents, isotonic agents, antiseptics and the like. The pharmaceutical formulation may contain the above described active ingredient in an amount of 1-95 % by weight, preferably 10-60 % by weight. The dose of the active ingredient may appropriately be selected depending on the objects of administration, administration route and conditions of the patients. The active ingredient is administered in doses between 1 mg and 800 mg per day in case of administration by injection and in doses between 10 mg and 5 g per day in case of oral administration. The preferred dose for injection is 20-200 mg per day and the preferred amount for oral administration 50-800 mg per day.

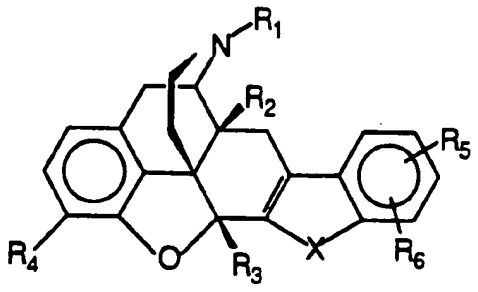
Biological studies

δ-Selective agonism was assessed using the electrical stimulated guinea-pig ileal longitudinal muscle preparations (GPI; containing m and k opioid receptors) (P.W. Schiller et al., Biochem. Biophys. Res. Commun., Vol. 58: 11-18, 1978; J. Di Maio et. al., J. Med. Chem., Vol. 25: 1432-1438, 1982) and mouse vas deferens preparation (MVD: containing μ, K and δ opioid receptors). The activities of the compounds to inhibit the contraction of the organs were measured. In the GPI, compounds 1 and 12 did not show inhibition of contraction up to 5.000 nM and 10.000 nM, respectively. These findings suggest that there is no agonist effect at m and k opioid receptors. In MVD, the tested compounds showed δ-selective agonism.

The biological studies of the novel morphinane derivatives of the formula (I) of the present invention have thus shown that these compounds have selectivity for δ opioid receptors and are effective as opioid agonists. Studies with δ-selective opioid agonists have shown that this class of compounds does not have dependence liability and produces substantially less respiratory depression than morphine. Dependence liability and respiratory depression are the most serious side effects of the opioid agonists used as analgesics (e.g. morphine). Accordingly, compounds according to the present invention useful as analgesics without showing the most serious side effects of opioid analgesics.

CLAIMS

1. A compound according to the formula (I)



(I)

wherein

R_1 represents C_1-C_6 alkyl or hydrogen

R_2 represents hydrogen, hydroxy,C_1-C_6 alkoxy; C_1-C_6 alkenyloxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 alkyloxy; C_7-C_{16} arylalkenyloxy wherein the aryl is C_6-C_{10} aryl and the alkenyloxy is C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy, C_1-C_6 alkenoyloxy, C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy;

R_3 represents hydrogen, C_1-C_6 alkyl; C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; hydroxy(C_1-C_6)alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2H; CO_2(C_1-C_6 alkyl);

R_4 is hydrogen, hydroxy; C_1-C_6 alkoxy; C_7-C_{16} arylalkyloxy wherein the aryl is C_6-C_{10} aryl and the alkyloxy is C_1-C_6 akyloxy; C_1-C_6 alkenyloxy; C_1-C_6 alkanoyloxy;

C_7-C_{16} arylalkanoyloxy wherein the aryl is C_6-C_{10} aryl and the alkanoyloxy is C_1-C_6 alkanoyloxy; alkyloxyalkoxy wherein alkyloxy is C_1-C_4 alkyloxy and alkoxy is C_1-C_6 alkoxy;

R_5 and R_6 each and independently represent hydrogen; OH; C_1-C_6 alkoxy; C_1-C_6 alkyl; hydroxyalkyl wherein the alkyl is C_1-C_6 alkyl; halo; nitro; cyano; thiocyanato; trifluoromethyl; CO_2H; $CO_2(C_1$-C_6 alkyl); $CONH_2$; $CONH(C_1$-C_6 alkyl); $CON(C_1$-C_6 alkyl)$_2$; amino; C_1-C_6 monoalkyl amino; C_1-C_6 dialkyl amino; C_5-C_6 cycloalkylamino; SH; SO_3H; $SO_3(C_1$-C_6 alkyl); $SO_2(C_1$-C_6 alkyl); SO_2 NH2; $SO_2NH(C_1$-C_6 alkyl); $SO_2NH(C_7$-C_{16} arylalkyl); $SO(C_1$-C_6 alkyl); or R_5 and R_6 together form a phenyl ring which may be unsubstituted or substituted by halo, nitro, cyano, thiocyanato; C_1-C_6 alkyl; trifluoromethyl; C_1-C_6 alkoxy, CO_2H, $CO(C_1$-C_6 alkyl), amino, C_1-C_6 monoalkylamino, C_1-C_6 dialkylamino, SH; SO_3H; H; $SO_3(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), $SO(C_1$-C_6 alkyl); and

X represents oxygen; sulfur; CH=CH; or NR_9 wherein R_9 is H, C_1-C_6 alkyl, C_1-C_6 alkenyl; C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; C_1-C_6 alkanoyl, and

wherein aryl is unsubstituted or mono-, di- or trisubstituted independently with hydroxy, halo, nitro, cyano, thiocyanato, trifluoromethyl, C_1-C_3 alkyl, C_1-C_3 alkoxy, CO_2H, $CONH_2$ $CO_2(C_1$-C_3 alkyl), $CONH(C_1$-C_3 alkyl), $CON(C_1$-C_3 alkyl)$_2$ $CO(C_1$-C_3 alkyl); amino; (C_1-C_3 monoalkyl)amino, (C_1-C_3 dialkyl)amino, C_5-C_6

cycloalkylamino, (C_1-C_3 alkanoyl)amido, SH, SO_3H, SO_3(C_1-C_3 alkyl), SO_2(C_1-C_3 alkyl), SO(C_1-C_3 alkyl), C_1-C_3 alkylthio or C_1-C_3 alkanoylthio;

with the proviso that when R_2 is hydroxy, R_3 cannot be hydrogen;

the compounds 6,7-Dehydro-4,5α-epoxy-3,14-dimethoxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-benzo[b]furano-morphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-17-methyl-7'-bromo-6,7-2',3'-indolomorphinan;

3,14-Diacetocy-6,7-dehydro-4,5α-epoxy-17-methyl-6,7-2',3'-indolomorphinan;

14-Acetoxy-6,7-dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;

14-Benzyloxy-6,7-dehydro-4,5α-epoxy-3-hydroxy-17-methyl-6,7-2',3'-benzo[b]furanomorphinan;
being excluded,

and the pharmacologically acceptable salts of the compounds of the formula (I).

2. A compound according to claim 1, wherein

R_1 is selected from hydrogen, methyl, ethyl, n-propyl or isopropyl;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy, benzyloxy substituted in the aromatic ring with F, Cl, NO_2, CN, CF_3, CH_3,OCH_3, allyloxy, cinnamyloxy or 3-phenylpropyloxy;

R_3 is selected from hydrogen, methyl, ethyl, benzyl or allyl;

R_4 is selected from hydroxy, methoxy, methoxymethoxy or acetyloxy;

R_5 and R_6 are each and independently selected from hydrogen, nitro, cyano, chloro, fluoro, bromo, trifluoromethyl, CO_2H, CO_2CH_3 $CONH_2$, $CONH$ CH_3 SH, SO_2NH_2, $N(CH_3)_2$ SO_2CH_3; and

X is selected from O, NH, NCH_3, N-benzyl or N-allyl.

3. A compound according to claim 1, wherein

R_1 is CH_3;

R_2 is selected from methoxy, ethoxy, n-propyloxy, benzyloxy or benzyloxy substituted in the aromatic ring with chlorine;

R_3 is selected from hydrogen or CH_3;

R_4 is hydroxy;

R_5 and R_6 are each and independently selected from hydrogen, CO_2H, $CONH_2$, SO_2NH_2, or SO_2CH_3; and

X is selected from O or NH.

4. A compound according to claim 1, being

6,7-Dehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-5,17-dimethyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3,14-dimethoxy-5,17-dimethyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5,17-dimethyl-6,7-2'3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3,14-dihydroxy-5,17-dimethyl-6,7-2'3'-indolomorphinan x HBr;

7,8-Dehydro-4,5α-epoxy-14-hydroxy-3-methoxy-5,17-dimethyl-6,7-2'3'-indolomorphinan x HBr;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-14-methoxy-5-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-3-hydroxy-5,17-dimethyl-14-n-propyloxy-6,7-2',3'-indolomorphinan methane sulfonate;

6,7-Dehydro-4,5α-epoxy-14-ethoxy-3-methoxy-17-methyl-6,7-2',3'-indolomorphinan;

6,7-Dehydro-4,5α-epoxy-14-ethoxy-17-isopropyl-3-methoxy-5-methyl-6,7-2',3'-benzo[b]furanomorphinan.

5. A compound according to claim 1 for use in therapy.

6. A compound according to claim 1 for use as an analgesic.

7. A compound according to claim 1, in form of a pharmaceutically acceptable salt.

8. A compound according to claim 7, wherein the salt is an inorganic salt.

9. A compound according to claim 6, wherein the salt is an organic salt.

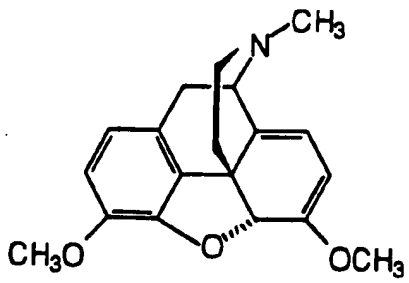
10. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of pain.

11. A pharmaceutical composition comprising a compound or a pharmacologically acceptable salt thereof according to claims 1-9 as an active ingredient, together with a pharmaceutically acceptable carrier.

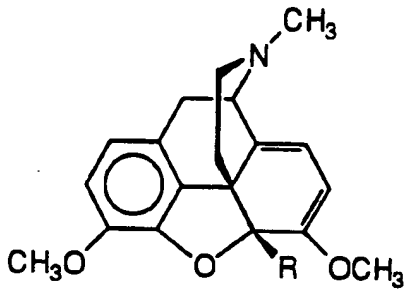
12. A method for the treatment of a subject suffering from pain, whereby an effective amount of a compound according to claims 1-9 is administered to a subject in need of such treatment.

13. A process for the preparation of a compound according to formula (I) of claim 1, wherein

A. i) thebaine of the formula



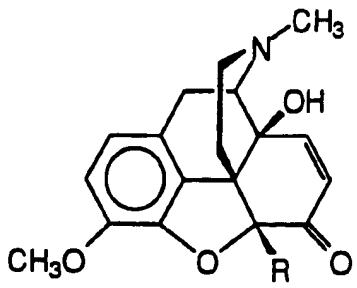
is being treated with dialkylsulfates, fluorosulfonic acid alkyl esters, alkylsulfonic acid alkyl esters, arylsulfonic acid alkylesters, alkyl halides, alkenyl halides, aralkyl halides, alkylsulfonic acid aralkyl esters, arylsulfonic acid aralkyl esters, arylalkenyl halides or chloroformates, giving compounds of the formula (II)



(II)

wherein R is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10} aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2 (C_1-C_6 alkyl);

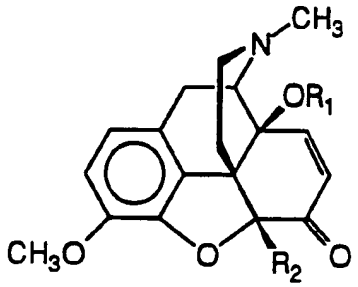
ii) (II) is reacted with performic acid or m-chloroperbenzoic acid at a temperature between 0 and 60 °C, giving compounds of the formula (III)



(III)

wherein R is as defined above or being hydrogen;

iii) the compounds (III) are thereafter being treated with dialkylsulfates, alkyl halides, alkenyl halides, arylalkyl halides, arylalkenyl halides or chloroformates , in the presence of a strong base and a solvent, giving compounds of the formula (IV)



(IV)

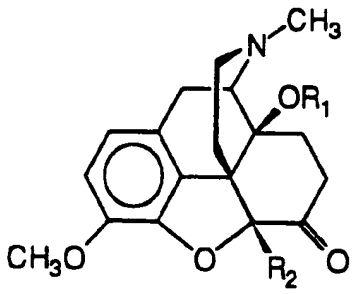
wherein R_1 is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{14} aryl and the alkenyl is C_1-C_6 alkenyl, C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_7-C_{16} arylalkenoyl wherein the aryl is C_6-C_{10} aryl and the alkenoyl is C_1-C_6 alkenoyl; and

R_2 is hydrogen; C_1-C_6 alkyl; C_1-C_6 alkenyl C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; C_7-C_{16} arylalkenyl wherein the aryl is C_6-C_{10}

aryl and the alkenyl is C_1-C_6 alkenyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

iv) the compounds (IV)

are reduced giving compounds of the formula (V)



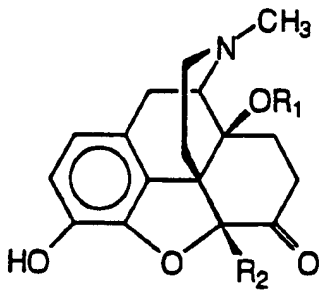
(V)

wherein

R_1 is C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkanoyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl;

R_2 is hydrogen; C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl; alkoxyalkyl wherein the alkoxy is C_1-C_6 alkoxy and the alkyl is C_1-C_6 alkyl; CO_2(C_1-C_6 alkyl);

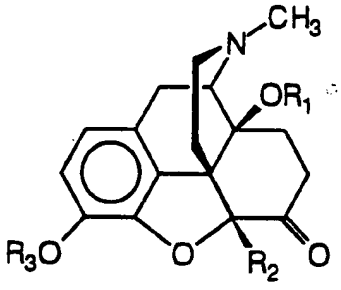
v) the compounds (V) are in turn challenged with reagents to achieve ether cleavage, giving phenolic compounds according to the formula (VI)



(VI)

wherein R_1 and R_2 are as defined above in formula (V);

vi) the compounds (VI) are thereafter alkylated or acylated giving compounds of the formula (VII)

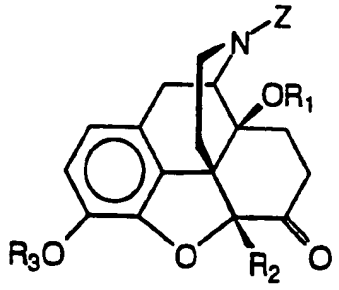


(VII)

wherein R_1 and R_2 are as defined above in formula (V), and

R_3 is C_1-C_6 alkyl, C_7-C_{16} arylalkyl wherein the aryl is C_6-C_{10} aryl and the alkyl is C_1-C_6 alkyl, C_1-C_6 alkenyl, C_7-C_{16} arylalkanoyl wherein the aryl is C_6-C_{10} aryl and the alkanoyl is C_1-C_6 alkanoyl, alkyloxyalkyl wherein alkyloxy is C_1-C_4 alkyloxy and alkyl is C_1-C_6 alkyl, C_1-C6 alkanoyl;

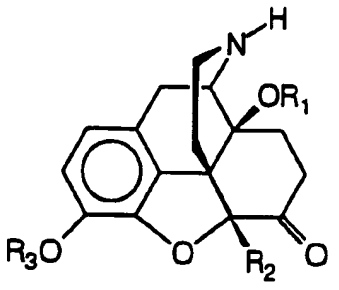
vii) the compounds (VII) are thereafter N-demethylated, employing chloroformates or cyanogen bromide giving the corresponding carbamates or N-cyano compounds of the formula (VIII)



(VIII)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII), and Z is CN, $CO_2CH{=}CH_2$, $CO_2CHClCH_3$, $CO_2CH_2CH_3$, CO_2 Ph or $CO_2CH_2CCl_3$;

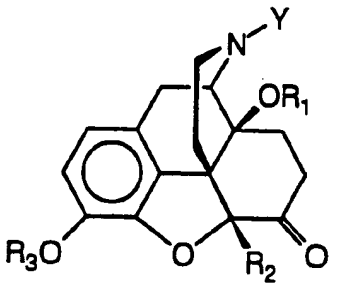
viii) the compounds (VIII) are cleaved giving compounds according to the formula (IX)



(IX)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII);

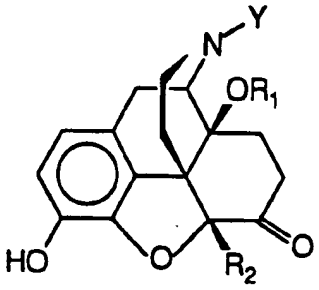
ix) the compounds (IX) are N-alkylated yielding compounds according to the formula (X)



(X)

wherein R_1, R_2 and R_3 are as defined above in formula (V) and (VII), and Y is methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, isopropyl, isobutyl, tert-butyl, 2-pentyl, 3-pentyl, 2-hexyl or 3-hexyl;

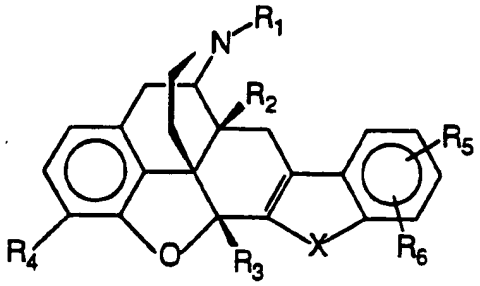
x) ether cleavage gives compounds according to the formula (XI)



(XI)

wherein R_1 and R_2 are as defined above in formula (V), and Y is as defined in formula (X) above;

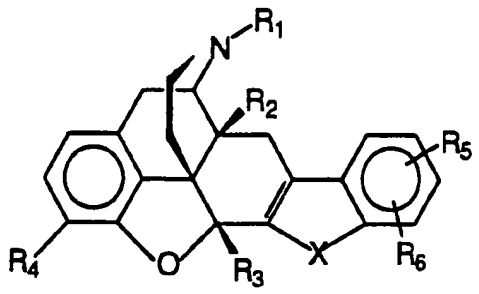
B) compounds of the formulas (VI), (VII), (IX), (X), (XI) or (XV) are reacted with phenylhydrazine or substituted phenylhydrazine giving compounds according to formula (I)



(I)

wherein R_3 is as defined above and X represents NH;

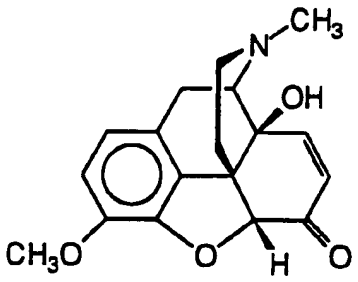
C) compounds of the formulas (VI), (VII), (IX),(X), (XI) or (XV) are reacted with O-phenylhydroxylamine or substituted O-phenylhydroxylamine, giving compounds of the formula (I)



(I)

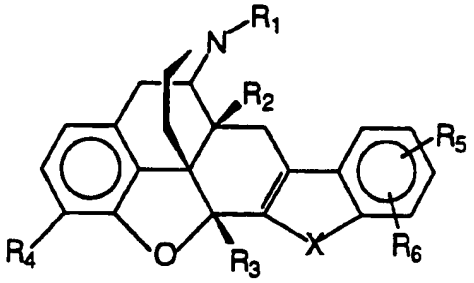
wherein R_3 is as defined above and X represents O;

D) thebaine is converted to 14-hydroxycodeinone according to formula (XII)



(XII)

which in turn is converted to compounds of the formula (I)



(I)

wherein R_1 and R_2 are as defined above and R_3 is hydrogen, with the proviso that R_2 cannot be hydroxy when R_3 is hydrogen.

14. A process according to claim 13, whereby the compound of the formula (II) of step ii) is reacted with performic acid at a temperature of 0-10°C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00504

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 489/09, C07D 491/18, A61K 31/485
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5223507 A (MICHAEL S. DAPPEN ET AL), 29 June 1993 (29.06.93), see especially compounds 11-13, 18-19	1-11,13
X	J. Med.Chem., Volume 35, 1992, P.S. Portoghese et al, "Opioid Agonist and Antagonist Activities of Morphindoles Related to Naltrindole", page 4325 - page 4329, see especially compounds 6 and 7	1-11,13
X	US 5225417 A (MICHAEL S. DAPPEN ET AL), 6 July 1993 (06.07.93)	1-11,13

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 1995	30 -08- 1995
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Göran Karlsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00504

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4816586 A (PHILIP S. PORTOGHESE), 28 March 1989 (28.03.89) -- --------	1-11,13

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/00504

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority; namely:
A method for treatment of the human or animal body by therapy, see rule 39.1.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/95

International application No.
PCT/SE 95/00504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 5223507	29/06/93	NONE	
US-A- 5225417	06/07/93	US-A- 5354863	11/10/94
US-A- 4816586	28/03/89	WO-A- 8900995	09/02/89